REMARKS

In view of the foregoing amendments and the following representations, reconsideration and allowance of the above-identified application is respectfully requested.

Applicants gratefully acknowledge the Examiner's withdraw of the rejection under 35 U.S.C. § 112 with respect to the term "thiazolidinedione derivative" and the rejection under 35 U.S.C. § 103(a) in view of Vergez et al., United States Published Patent Application No. 2006/0204578.

Claims 1-4, 7-14, 17-20 and 31-34 are pending in the present application.

35 U.S.C. § 112

On page 3 of the Office Action, the Examiner rejected claims 3 and 13 under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner rejected the claims because the phrase "optionally a secondary seal coat surrounding the core" is unclear. Although Applicants believe the phrase is clear, in an effort to expedite prosecution, Applicants have amended claims 1, 3, 11 and 13 to more clearly recite the invention. Amended claims 1 and 11 recite a dosage form with three main elements: (1) a controlled release metformin core; (2) a primary seal coat around the core; and (3) an immediate release pioglitazone layer applied to the primary seal coat. The present amendments to claims 1 and 11 further define the controlled release metformin core a consisting of: (i) a mixture of metformin and at least one pharmaceutically acceptable excipient; (ii) an optional secondary seal coat surrounding

the metformin mixture; and (iii) a semi permeable membrane surrounding the metformin mixture or if present the optional secondary seal coat. Claims 3 and 13 have been amended to track the amendments to claims 1 and 11. No new matter is added by these amendments. Support can be found on page 4, lines 23-31, page 5, lines 13-27, page 6, line 13 to page 7, line 8 and Examples 1-6 on pages 12-25 of the specification.

Applicants have also amended claim 1 as suggested by the Examiner to replace the period on line 5 of the claim with a semicolon. Applicants have further amended claims 1, 11 and 31 to correct the description of the pioglitazone salts.

Based upon the foregoing amendments, it is respectfully requested that the rejection of the claims under 35 U.S.C. § 112, second paragraph, be withdrawn.

35 U.S.C. § 103(a)

On page 6 of the Office Action, the Examiner rejected claims 1-16 under 35 U.S.C. § 103(a) as being unpatentable over the teachings of Cutie et al., WO 01/82875 ("Cutie") in view of Lewis, WO 01/35940 ("Lewis").

On page 11 of the Office Action, the Examiner rejected claims 1-16 under 35 U.S.C. as being unpatentable over Cutie in view of Lewis and in further view of Vergez et al., United States Published Patent Application No. 2006/0204578 (Vergez).

Based upon the detailed discussion of the rejections provided by the Examiner, the Applicants have assumed the recitation of only claims 1-16 in the rejections was an inadvertent typographical error.

Applicants respectfully traverse the rejections under 35 U.S.C. 103(a) in view of the

currently amended the claims.

As indicated above in the discussion of the 35 U.S.C. § 112 rejection, the present claims require a controlled release metformin core coated with a semi permeable membrane. The semi permeable membrane is subsequently coated with a primary seal coating. The primary seal coating is subsequently coated with an immediate release pioglitazone coating. As explained in the prior submissions, Applicants discovered a primary seal coating applied to the semi permeable membrane was necessary to insure proper adhesion of the pioglitazone layer and also to assist in the proper release of the pioglitazone from the dosage form. The unique structure recited in the pending claims is not disclosed or suggested by the cited prior art.

Cutie discloses a dosage form that combines metformin and pioglitazone. The exact structure of the dosage form taught by Cutie is unclear at best. For example on page page 2 lines 20-30, Cutie describes the dosage form as follows:

> As indicated above, the relative concentrations of each drug is such that a first layer comprising metformin is prepared. The first layer covers at least a portion of a core comprising metformin...The first layer should comprise pioglitazone hydrochloride because its dose requirement is lower compared to metformin.

From this description, it is unclear which drug is present in the core and which drug is present in the first layer. Cutie also describes dosage forms that are inaccordance with the alleged invention as follows:

> The subject core formulation of the invention may contain other various materials which modify the physical form of the dosage unit (the subject core formulation), for example, as coatings. Thus, the subject core formulation of the present invention may be coated with sugar, shellac or other enteric coating agents...
>
> In an alternative embodiment of the present invention. The resultant core

formulation (having a first layer completely or partially covering the core), is treated whereby an outer shell, at least a portion of which comprises a biodegradable material having a predetermined rate of degradation or metabolism in the host being treated, is formed which encloses the particles of the first layer and or the core....

The shell encapsulating the particles of pioglitazone hydrochloride of the first layer and/or the particles of metformin of the core is obtained by any conventional microencapsulation process whereby microspheres of metformin and/or pioglitazone are formed.

In a variation of the above alternative embodiment, the resultant core formulation is treated whereby only the top surface area of the first layer comprising metformin has a shell coating thereon. In this regard, reference is made to U.S. Patent No. 5,916,584, incorporated hereinto by reference in its entirety, which describes the process for forming such as shell. The resulting core formulation having the first layer encapsulated by the shell comprising the shell material, is one which provides a delay time prior to release of the active ingredients, i.e pioglitazone hydrochloride and metformin, to the patient being treated for diabetes mellitus.

Page 7, line 7 to page 8, line 14 of Cutie. Based upon the above description and the claims of Cutie, Applicants believe that Cutie is describing a dosage form wherein the pioglitazone layer is applied directly to a metformin core. The pioglitazone coated metformin core may be further coated with an enteric or shell of biodegradable material to delay or control the release of both the metformin and pioglitazone.

Applicants respectfully submit the present claims are vastly different from the dosage form suggested by Cutie. The presently claimed dosage form requires controlled release of only metformin and immediate release of the pioglitazone. In addition, the presently claimed dosage form requires a primary seal coat between the semi permeable membrane of the controlled release metformin core and the immediate release pioglitazone layer. Cutie does not suggest a dosage form with a primary seal coat between the immediate release piogiltiazone and the semi permeable membrane of the

controlled release metformin core.

The addition of the Lewis reference to Cutie does not overcome the deficiencies of Cutie.

Lewis discloses an immediate release metformin and pioglitazone composition wherein the metformin is mixed with conventional binding agents. *See*: page 4, lines 29-43 and the examples on page 7 of Lewis. This immediate release metformin core is coated with a barrier coating that is subsequently coated with an immediate release pioglitazone layer.

There is no mention or disclosure of a controlled release metformin core in Lewis. More importantly, there is no mention or disclosure of a controlled release metformin core with a semi permeable membrane in Lewis. Therefore, a person of ordinary skill in the art viewing both Cutie and Lewis would be lead to a dosage form wherein a barrier layer is inserted between the immediate release metformin core and the immediate release first pioglitazone. This three layer core structure would then be coated with an enteric or biodegradable material as taught by Cutie to delay or control the release of both drugs.

The addition of Vergez to both Cutie and Lewis would also not lead an individual of ordinary skill in the art to the present invention. Rather, the addition of Vergez would only confirm the afore-described combination product of Cutie and Lewis which releases both the metformin and pioglitazone in a delayed or controlled manner.

Vergez requires controlled release of two active ingredients. This teaching is similar to the teachings of Cutie. *See*: Vergez, ¶ 2 ("This invention pertains to a dosage

form that provides a controlled release of two different drugs."); ¶ 15 ("The present invention provides an oral dosage form that provides a controlled release device of two or more different agents"); ¶ 70 ("Neither one of the compositions in the core is intended for rapid release of active agent"); and ¶ 73 ("Neither of the first or second active agents is released rapidly from the core").

Applicants respectfully submit that the combined teachings of Cutie and Lewis or the combined teachings of Cutie, Lewis and Vergez would not lead an individual of ordinary skill to the dosage form recited in the pending claims. The presently amended claims recite a dosage form that comprises a semi permeable membrane coated controlled release metformin core, a rapidly dissolving or dispersible primary seal coat and an immediate release pioglitazone coat applied to the primary seal coat wherein the metformin is the only active ingredient released in a controlled manner and the pioglitazone is released immediately.

Based upon the foregoing amendments and representations, it is respectfully submitted that the pending claims are patentable over the cited references because the pending claims require a semipermeable membrane coated controlled release metformin core and an immediate release pioglitazone coating applied to a rapidly dissolving or disintegrating primary seal coat. This unique metformin/pioglitazone dosage form is not suggested or disclosed by Cutie, Lewis and/or Vergez.

DOUBLE PATENTING

On page 3 of the Office Action, the Examiner maintained the provisional non-statutory obviousness-type double patenting rejection of claims 1, 2, 4 and 8-10 in view of claims 1, 20 and 33-40 of co-pending United States Patent Application No. 11/094,493.

Applicants believe the provision of MPEP § 804(I)(B)(1) are applicable to the present situation as explained in the prior submission. In addition, Applicants respectfully submit the provisional double patenting rejection should be withdrawn because the currently pending claims of Application No. 11/094,493 are patentably distinct from the present claims. The claims of 11/094,493 were amended on January 31, 2008 to specifically recite the immediate release pioglitazone layer comprising pioglitazone, a surfactant and a disintegrating agent. As explained in the January 31, 2008 amendment this unique combination of pioglitazone, surfactant and disintegrating agent produced an unexpected increase in the bioavailabilty of the pioglitazone. A copy of the January 31, 2008 amendment is attached hereto as Exhibit A for the Examiner's convenience. In light of the amendment to the present claims, the January 31, 2008 amendment to the claims of 11/094,493 and the completely unexpected improvement in pioglitazone bioavailabilty obtained by the dosage form recited in the claims of 11/094,493, Applicants respectfully request reconsideration and withdrawal of the provisional double patenting rejection.

Based upon the foregoing amendments and representations, Applicants respectfully requested that the rejection of the claims in the above-identified application be withdrawn. Early and favorable action is earnestly solicited.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450 on June 25, 2008

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